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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,166	11/17/2000	Douglas A. Treco	10278-014001	6951
26161	7590	04/06/2005	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			JIANG, DONG	
			ART UNIT	PAPER NUMBER

1646

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/716,166

Applicant(s)

TRECO ET AL.

Examiner

Dong Jiang

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 December 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-6, 8-14, 17, 19, 21-46 and 83-93 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-14, 17, 19, 21-46 and 83-93 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

*lit*

### **DETAILED OFFICE ACTION**

Applicant's response filed on 06 December 2004 is acknowledged.

Currently, claims 1-6, 8-14, 17, 19, 21-46 and 83-93 are pending and under consideration.

#### **Rejections Over Prior Art:**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 8-13 remain rejected, and claims 90 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants), Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), and Patel et al. (CIBA Foundation Symposium, 1995, 190: 26-50), for the reasons of record set forth in the previous Office Actions mailed on 09 September 2003, and 03 June 2004, respectively.

Applicants argument filed on 06 December 2004 has been fully considered, but is not deemed persuasive for reasons below.

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At page 2 of the response, the applicant made similar argument as that in the last response filed on 05 March 2004, that the Office has failed to establish a prima facie case of obviousness against the claims as it does not identify a suggestion or motivation leading to combine the teachings of the five cited references, and fails to demonstrate a reasonable expectation of success. Applicants further point out, at pages 3-5, what each reference does not teach, such as that Habener does not teach, suggest or provide any guidance for linking GLP-1 to any peptide domains, Suzuki discloses no teaching or suggestion to link GLP-1 to a eukaryotic signal sequence and somatostatin pro-region, Sevarino does not teach or suggest linking a somatostatin prepro-region to a non-somatostatin peptide, and Stoller contains no teaching or suggestion to link a somatostatin prepro-region to a small non-somatostatin peptide, and applicants argue that these are isolated references with absolute no suggestion of combination, which comes entirely and only with hindsight guided by applicants disclosure. This argument is not persuasive for the following reasons.

In response to applicant's argument that there is no suggestion to combine the references, as addressed in the last Office Action, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In instant situation, besides the therapeutic reasons for making GLP-1 taught by Habener, both Sevarino and Stoller teach an expressing vector comprising nucleic acid sequences encoding the prepro-region of a preprosomatostatin and a heterologous polypeptide, which would allow the target peptide to be secreted, greatly facilitating the purification process. The combination of therapeutic use of GLP-1 and advantages of using an expressing vector comprising nucleic acid sequences encoding the prepro-region of a preprosomatostatin to make a heterologous polypeptide taught by the cited references provides provide strong motivation to make the construct as claimed.

With respect to reasonable expectation of success, as addressed in the last Office Action, the requirement for such does *not* rest on a *complete certainty* of success. A prior art reference only needs to provide an indication of a *reasonable expectation* of success. In the instant case,

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Sevarino and Stoller have independently demonstrated successful expression of two different heterologous peptides by fusing pro-region of prosomatostatin with the target peptide, which would be considered by one of ordinary skill in the art to be sufficient for indicating a *reasonable expectation* of success for the expression of other heterologous peptides.

With respect to applicants argument as to what each of the references does not teach, as addressed in the last Office Action, the argument is against the references individually. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, it is the combined *teachings* (rather than what is not taught) provide the motivation for making the construct as claimed. The test for obviousness is not that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*.

In response to applicant's argument that the suggestion to combine the isolated references comes entirely and only with hindsight guided by applicants disclosure, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

At page 5 of the response, the applicant argue that the Office has not explained why a skilled artisan would have been motivated to combine Sevarino and Stoller, which relate to the prepro-region of somatostatin precursor and its role in directing transport through the regulated secretory pathway of endocrine cells. This argument is not persuasive because the fact that somatostatin is a secreted hormone is self-evident that the prepro-region of somatostatin is responsible for the secretion, and the mechanism of regulation of secretory pathway is irrelevant to the prior art rejection.

At pages 6-7 of the response, the applicant argue that the combined results of Sevarino and Stoller, amount to only two prepro-region containing chimeras, neither of which includes a small, non-somatostatin peptide, that thus, they would not have created a reasonable expectation

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that such could successfully be made and used for expressing small non-somatostatin peptides. Applicants further argue that the successful swapping of homologous somatostatin domains (by Sevarino) simply would not have suggested that non-homologous small peptides could be successfully be used, and that successful expression of a large peptide (as by Stoller) does not fairly suggest that the same expression system can be used to direct the expression of small peptides. This argument is not persuasive because the key point here is that Sevarino and Stoller successfully and independently used the same system to express *distinct peptides*, which share neither sequence homology nor molecular size, indicating that neither sequence homologous or the size of a molecule to be expressed is critical in this expression system. Given the fact that GLP-1, like somatostatin, is a small peptide hormone, and that sequence homology does not seem to play a role as to the expression in this system, it is more likely than not that GLP-1 would be expressed successfully in the system in the absence of any indication to the contrary. Therefore, the combined references indeed provide a *reasonable expectation* of success. Further, if Sevarino or Stoller had taught the expression of small non-somatostatin peptides, the present claims would have been *anticipated*.

At pages 7-8 of the response, the applicant argue that it appears that the Office has done no more than piece the invention together using applicants specification for at least the knowledge, or as a template, which constitutes impermissible hindsight. This argument is not persuasive because all knowledge used by the examiner in the rejection is cited from the teachings of the prior art references, which were available prior to applicants disclosure. With respect to the argument of "hindsight", as addressed in the last Office Action and above, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

Claims 14, 17, 19, 21-35, 37-46, and 83-89 remain rejected, and claims 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), and in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants),

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Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), and Patel et al. (CIBA Foundation Symposium, 1995, 190: 26-50), as applied to claims 1-6 and 8-13 above, and further in view of Warren et al. (Cell, 1984, 39(3 Pt2): 547-55), and Selden et al., US 6,531,124 B1, for the reasons of record set forth in the previous Office Actions mailed on 09 September 2003, and 03 June 2004, respectively.

Applicants argument with respect to “non-endocrine cell” claims filed on 06 December 2004 has been fully considered, but is not deemed persuasive for reasons below.

At pages 8-9 of the response, the applicant argues, besides the similar argument above, that the Office has not supplied the required motivation and reasonable expectation of success for combine seven references to arrive at the rejected claims. In response to applicant’s argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Applicants further argue, at page 9 of the response, that Selden discloses expressing GLP-1 using a primary cell transfected with a DNA encoding GLP-1 does not provide suggestion or motivation to produce the claimed cell having the specific recited construct, and that the successful operation of one expression system in a cell line does not indicate a reasonable expectation for success of an unrelated expression system. This argument is not persuasive because, with the exception of claims 21 and 42, the limitation regarding to primary cells is not present in the claims. Further, applicants argument requires more of the references than their own specification discloses, i.e., the present specification never discloses the use of primary cells.

At pages 10 of the response, the applicant argues that the Warren and Patel references teach away from the present invention as the Warren reference indicates that the data show a relatively low level of SRIF secreted compared to insulin secretion in AtT-20 cells, which suggest *very low* levels of processed somatostatin in non-endocrine cell. This argument is not persuasive because “*very low levels*” is merely applicants own interpretation, and Warren’s “*relatively low level ... compared to ...*” is not the same as applicants “*very low levels*”. Further, as addressed in the previous Office Action, the Warren reference clearly states that “however, in the absence of quantitative data we cannot accurately compare either the levels of

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proteolytic processing or secretion of the two hormones in these different cell types”, indicating that it is improper to compare the two levels, nor draw any conclusion as to the secretion levels because the result is not quantitative. Therefore, the prior art teachings do not constitute “teaching away”. Applicants further argue that Warren did not observe cleavage of proSIRF to SS-28, suggesting the COS cell processing does not reflect the true physiological processing of preproSIRF. This argument is not persuasive because Warren’s SIRF is from fish, which have two distinct somatostatin genes encoding for separate SS-14 and SS-28, as indicated by Warren that angler fish SS-28 was shown to be derived only from preproSRIF II (page 553, the right column). As such, Warren concludes, contrary to that by applicants, that absence of SS-28 in these transfected COS cells suggests that the COS cell processing *does* reflect the true physiological processing of preproSIRF (page 553, the right column).

At pages 11 of the response, the applicant argues that Warren’s method of detection (HPLC) indicates low level processed propeptides expressed. This argument is not persuasive because this is irrelevant as the present claims do not have any limitation as to the level of expression, and Warren’s teaching of the expression system and use of non-endocrine cell reads on the present claims. The only difference is that Warren’s target peptide is a fish SRIF, and the target peptide of the present invention is a non-somatostatin peptide, which sequence difference, as addressed above, does not seem to be important. The important message from Warren is that that COS cell contain the necessary proteolytic processing enzymes to convert preprosomatostatin to the mature hormone and the cellular apparatus necessary for its secretion (the abstract), and that the COS cell processing reflects the true physiological processing of preproSIRF, which clearly provides reasonable expectation of success regarding the expression of the recited construct in a non-endocrine cells as claimed. Applicants further argue that the Patel reference shows that somatostatin was processed much less effectively in COS cells relative to endocrine cells, therefore, teaches away from the effectiveness of processed somatostatin expression in non-endocrine cells. This argument is not persuasive because it is irrelevant for the same reasons above as the present claims do not require any specific levels of expression, thus read no difference from the teachings of the prior art.



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Claim 36 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), and in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55), and Warren et al. (Cell, 1984, 39(3 Pt2): 547-55), as applied to claims 14, 17, 19, 21-35, 37-46 and 83-89 above, and further in view of Nagai et al., US 6,010,883, for the reasons of record set forth in the last Office Actions mailed on 03 June 2004.

Applicants argument with respect to “non-endocrine cell” claims filed on 06 December 2004 has been fully considered, but is not deemed persuasive for reasons below.

At page 12 of the response, the applicant argues that for the same reasons above, Sevarino, Stoller, and Warren do not render obvious a non-endocrine cell comprising recited construct, and that Nagai does not remedy the deficiencies of Sevarino, Stoller, and Warren, and provides neither motivation nor the requisite expectation for success. This argument is not persuasive for the same reason addressed above.

**Conclusion:**

No claim is allowed.

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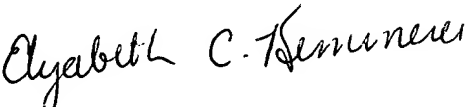
**Advisory Information:**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

  
**ELIZABETH KEMMERER  
PRIMARY EXAMINER**

Dong Jiang, Ph.D.  
Patent Examiner  
AU1646  
3/30/05